ORIGINAL ARTICLE

Ketamine or Etomidate for Tracheal Intubation of Critically Ill Adults

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ABSTRACT

BACKGROUND

For critically ill adults undergoing tracheal intubation, observational studies suggest that the use of etomidate to induce anesthesia may increase the risk of death. Whether the use of ketamine rather than etomidate decreases the risk of death is uncertain.

METHODS

In a randomized trial conducted in 14 emergency departments and intensive care units in the United States, we randomly assigned critically ill adults who were undergoing tracheal intubation to receive ketamine or etomidate for the induction of anesthesia. The primary outcome was in-hospital death from any cause by day 28. The secondary outcome was cardiovascular collapse during intubation, defined by the occurrence of a systolic blood pressure below 65 mm Hg, receipt of a new or increased dose of vasopressors, or cardiac arrest.

RESULTS

A total of 2365 patients underwent randomization and were included in the trial population; 1176 were assigned to the ketamine group and 1189 to the etomidate group. In-hospital death by day 28 occurred in 330 of 1173 patients (28.1%) in the ketamine group and in 345 of 1186 patients (29.1%) in the etomidate group (risk difference adjusted for trial site, −0.8 percentage points; 95% confidence interval [CI], −4.5 to 2.9; P=0.65). Cardiovascular collapse during intubation occurred in 260 of 1176 patients (22.1%) in the ketamine group and in 202 of 1189 patients (17.0%) in the etomidate group (risk difference, 5.1 percentage points; 95% CI, 1.9 to 8.3). Prespecified safety outcomes were similar in the two groups.

CONCLUSIONS

Among critically ill adults undergoing tracheal intubation, the use of ketamine to induce anesthesia did not result in a significantly lower incidence of in-hospital death by day 28 than etomidate. (Funded by the Patient-Centered Outcomes Research Institute and others; RSI ClinicalTrials.gov number, NCT05277896.)

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*A full list of the RSI investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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More than 13 million critically ill adults undergo emergency tracheal intubation worldwide each year,[1,2] and approximately 30% of these patients die before hospital discharge.[3,4] Nearly all patients undergoing tracheal intubation in an emergency department (ED) or intensive care unit (ICU) receive a medication to induce anesthesia for the procedure.[3,4] Whether the choice of induction medication for critically ill adults affects the risk of death or other outcomes is uncertain.

Etomidate is the medication most often used to induce anesthesia during emergency tracheal intubation in the United States.[4-10] This imidazole-derived sedative–hypnotic agent, which acts on γ-aminobutyric acid receptors, has been described as an ideal induction medication for critically ill adults because of its rapid onset and limited effect on blood pressure and heart rate.[11-13] However, etomidate inhibits 11β-hydroxylase in the adrenal glands, and a single dose decreases cortisol production for up to 72 hours.[14-19] Concern that etomidate-induced corticosteroid insufficiency may cause organ dysfunction and death,[7,17] particularly in patients with sepsis,[20-22] has led regulators to remove etomidate from the market in multiple countries.[23-25]

Ketamine, a dissociative agent that acts on *N*-methyl-D-aspartate receptors and does not impair cortisol production, is an increasingly used alternative to etomidate for induction of anesthesia in critically ill patients.[7,26,27] Because its administration increases plasma catecholamine concentrations, ketamine has been postulated to maintain hemodynamic stability during intubation better than other induction medications.[24,28,29] However, ketamine is also a negative inotrope and vasodilator,[30-32] and observational studies have shown an association between the receipt of ketamine and hypotension,[26,33-35] arrhythmia,[36,37] and cardiac arrest during intubation.[38-40]

Previous small and moderate-sized randomized trials and meta-analyses in which ketamine was compared with etomidate have shown conflicting results, with some suggesting that the use of ketamine decreases the risk of death[41-43] and others showing no marked differences in outcomes.[18,44,45] To determine the effects of the use of ketamine, as compared with etomidate, for induction of anesthesia during emergency tracheal intubation, we conducted the Randomized Trial of Sedative Choice for Intubation (RSI). We hypothesized that the use of ketamine would decrease the incidence of death.

METHODS

TRIAL DESIGN AND OVERSIGHT

The Pragmatic Critical Care Research Group[4,8,46] conducted this pragmatic, multicenter, unblinded, randomized, parallel-group trial in which the use of ketamine was compared with the use of etomidate for induction of anesthesia during emergency tracheal intubation of critically ill adults. The trial was initiated by the investigators and approved by the institutional review board at Vanderbilt University Medical Center and the Food and Drug Administration. The trial was conducted under the exception from informed-consent requirements for emergency research; details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.[47] The trial was registered at ClinicalTrials.gov before initiation and was overseen by an independent data and safety monitoring board. The trial protocol and statistical analysis plan, available at NEJM.org, were published before the conclusion of enrollment.[48] The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The funding institutions had no role in the conception, design, or conduct of the trial; the collection, management, analysis, interpretation, or presentation of the data; or the preparation, review, or approval of the manuscript.

TRIAL SITES AND PATIENT POPULATION

The trial was conducted at 14 sites (6 EDs and 8 ICUs) in 6 medical centers across the United States. Critically ill patients 18 years of age or older who were undergoing tracheal intubation with the use of a medication to induce anesthesia were eligible. Patients were excluded if they were known to be pregnant, were known to be prisoners, were presenting with a primary diagnosis of trauma, or had an immediate need for tracheal intubation that precluded randomization. Patients were also excluded if the treating clinicians determined that the use of ketamine or etomidate was either necessary or contraindicated. Details of the trial sites and a complete list of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

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RANDOMIZATION

Patients were randomly assigned in a 1:1 ratio to receive ketamine or etomidate for the induction of anesthesia during tracheal intubation. Randomization was performed with the use of permuted blocks of variable size and was stratified according to trial site. The trial-group assignments were placed in sequentially numbered, opaque envelopes and remained concealed until after enrollment. Clinicians and research personnel were aware of the trial-group assignments after randomization.

INTERVENTIONS

For patients assigned to the ketamine group, clinicians were instructed to administer ketamine intravenously to induce anesthesia for tracheal intubation. A nomogram provided a list of doses of ketamine (in milligrams) that was based on patient weight, which corresponded to a full dose (2.0 mg per kilogram of body weight), an intermediate dose (1.5 mg per kilogram), or a reduced dose (1.0 mg per kilogram) (details are provided in the Supplementary Appendix).[49] Clinicians selected the dose of ketamine to administer.

For patients assigned to the etomidate group, clinicians were instructed to administer etomidate intravenously to induce anesthesia for tracheal intubation. A nomogram provided a list of doses of etomidate (in milligrams) that was based on patient weight, which corresponded to a full dose (0.3 mg per kilogram), an intermediate dose (0.25 mg per kilogram), or a reduced dose (0.2 mg per kilogram) (details are provided in the Supplementary Appendix). Clinicians selected the dose of etomidate to administer.

All other aspects of the patients' medical care were at the discretion of the treating clinicians, including the administration of vasopressors before induction, the choice of neuromuscular blocking agent for intubation, the approach to sedation and analgesia during mechanical ventilation, and the administration of intravenous fluids, vasopressors, and systemic glucocorticoids.

DATA COLLECTION

A trained observer who was not involved in the performance of the intubation collected data on the duration of intubation, the systolic blood pressure, and the administration of vasopressors during the interval between induction of anesthesia and 2 minutes after intubation. Immediately after intubation, clinicians reported whether the patient had arrhythmia or cardiac arrest between the time of induction of anesthesia and 2 minutes after intubation. Trial personnel reviewed the medical record to collect data on the patients' baseline characteristics, periprocedural care, and clinical outcomes. They collected information on death from the medical record, from publicly available vital statistics records, and during follow-up telephone calls with patients or family members at 3 and 12 months (details are provided in the Supplemental Methods section of the Supplementary Appendix).

OUTCOMES

The primary outcome was in-hospital death by day 28, which was defined as death from any cause occurring between enrollment and 28 days after enrollment, with outcome ascertainment ending at hospital discharge. The single prespecified secondary outcome was cardiovascular collapse during intubation, which was defined by the occurrence of any of the following events during the interval between induction of anesthesia and 2 minutes after tracheal intubation: a systolic blood pressure below 65 mm Hg, receipt of a new or increased dose of vasopressors, or cardiac arrest. Exploratory procedural outcomes included the lowest systolic blood pressure, a lowest systolic blood pressure below 80 mm Hg, a highest systolic blood pressure above 180 mm Hg, the lowest oxygen saturation, and a lowest oxygen saturation below 80% — all of which were assessed during the interval between induction of anesthesia and 2 minutes after intubation — as well as successful intubation on the first attempt and the time from induction of anesthesia to intubation. Exploratory clinical outcomes were the number of ventilator-free days, vasopressor-free days, and ICU-free days. Safety outcomes included the systolic blood pressure at 24 hours after enrollment and ongoing receipt of vasopressors at 24 hours. A full list of the trial outcomes, including additional details, is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Details regarding the determination of the sample size have been reported previously[48] and are included in the Supplementary Appendix. Assuming an incidence of in-hospital death by day 28 of 30.0% in the etomidate group,[4,8] 80% statistical

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power, and a two-sided alpha level of 0.05, we calculated that 2308 patients would need to be enrolled to detect an absolute difference of 5.2 percentage points between the groups in the incidence of in-hospital death by day 28. To ensure adequate power if data were missing in up to 3% of the patients, we planned to enroll a total of 2364 patients (1182 per group). The trial protocol included a single interim analysis, which was planned to be performed after 1182 patients had been enrolled; a P value threshold of 0.001 or less was to be used for the difference between the groups in the primary outcome that would justify stopping the trial. On the basis of the results of the interim analysis, the data and safety monitoring board recommended that the trial continue without modification.

The primary analysis was an intention-to-treat comparison of the primary outcome in the ketamine and etomidate groups that was performed with the use of a generalized linear mixed-effects model with a random effect for trial site and a fixed effect for trial-group assignment (ketamine group vs. etomidate group) without adjustment for covariates. The primary analysis included all the patients who had undergone randomization, except for those who had withdrawn from follow-up before ascertainment of the primary outcome. Sensitivity analyses of the primary outcome included the following: an unadjusted analysis that was performed with the use of a chi-square test; an analysis with adjustment for prespecified baseline covariates; analyses in which patients who had withdrawn before outcome ascertainment were classified as having died in the hospital by day 28 (the primary outcome) or as not having died in the hospital by day 28; an analysis of death by day 28 in any location (i.e., including both in-hospital deaths and deaths that occurred after hospital discharge); and an analysis of survival through day 28 in any location with the use of the Kaplan–Meier method (details are provided in the Supplementary Appendix).

In accordance with published guidelines,[50,51] we examined whether prespecified baseline variables modified the effect of the trial-group assignment on the primary outcome with three approaches. The first approach involved subgroup analyses that used a generalized linear mixed-effects model with a random effect for trial site and fixed effects for trial group, the proposed effect modifier, and the interaction between the effect modifier and the trial group, without adjustment for covariates. The second was a risk-modeling approach, in which previously validated models for the baseline risk of in-hospital death by day 28 were used.[52] The third was an effect-modeling approach that used a machine-learning model to predict the effect of ketamine, as compared with etomidate, on the primary outcome for each patient on the basis of the patient's individual characteristics (individualized treatment effect).[53,54] Details of these analyses are provided in the Supplementary Appendix.

Secondary and exploratory outcomes were compared in the two trial groups with the use of a chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous or ordinal variables; between-group differences are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two groups. All the analyses were performed with the use of R software, version 4.4.2 (R Foundation for Statistical Computing).

RESULTS

PATIENTS

Between April 6, 2022, and August 10, 2025, a total of 3439 patients were assessed for eligibility, of whom 2367 (68.8%) were enrolled and underwent randomization. The reasons for exclusion are listed in Figure S1 in the Supplementary Appendix. Two patients who were identified after enrollment as being prisoners were excluded from all analyses. The remaining 2365 patients were included in the trial population. The median age of the patients was 60 years, 46.7% had sepsis or septic shock, and 22.0% were receiving vasopressors (Table 1). Tracheal intubation was performed in an ED for 55.7% of the patients and in an ICU for 44.3% of the patients (Table S1). A total of 1176 patients were assigned to the ketamine group, and 1189 patients were assigned to the etomidate group (Tables S2 through S6). Six patients discontinued follow-up before day 28, and analyses of outcomes at day 28 included 1173 patients in the ketamine group and 1186 patients in the etomidate group. The representativeness of the trial population is described in the Supplementary Appendix.

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MEDICATIONS FOR TRACHEAL INTUBATION

Of the 1176 patients in the ketamine group, 1167 (99.2%) received ketamine, and 1184 of the 1189 patients in the etomidate group (99.6%) received etomidate (Table 2 and Tables S7 and S8). The median dose of ketamine was 140 mg (interquartile range, 100 to 150), which was equivalent to 1.6 mg per kilogram (interquartile range, 1.4 to 2.0) (Fig. S2). The median dose of etomidate was 20 mg (interquartile range, 20 to 25), which was equivalent to 0.28 mg per kilogram (interquartile range, 0.24 to 0.31). Approximately 2% of the patients in each group received propofol, benzodiazepines, or opiates during the induction of anesthesia. A total of 99.7% of the patients in each of the two groups received a neuromuscular blocking agent (Table S9). Additional characteristics of the tracheal intubation procedure are shown in Table 2 and Tables S10 and S11.

PRIMARY OUTCOME

In-hospital death by day 28 occurred in 330 of 1173 patients (28.1%) in the ketamine group and in 345 of 1186 patients (29.1%) in the etomidate group (risk difference adjusted for trial site, −0.8 percentage points; 95% confidence interval [CI], −4.5 to 2.9; P=0.65) (Fig. 1 and Table 3). Death in any location by day 28 (one of the sensitivity analyses) occurred in 378 of 1173 patients (32.2%) in the ketamine group and in 384 of 1186 patients (32.4%) in the etomidate group (risk difference adjusted for trial site, 0.0 percentage points; 95% CI, −3.9 to 3.9). All the sensitivity analyses showed results similar to those of the main analysis (Fig. S3 and Tables S12 and S13), as did the subgroup analyses (Fig. 2 and Fig. S4), including the analysis of the subgroup comprising the 1101 patients with sepsis or septic shock (in-hospital death occurred in 38.8% of the patients in the ketamine group and in 38.2% of those in the etomidate group; risk difference adjusted for trial site, 1.0 percentage points; 95% CI, −4.8 to 6.7). Risk-modeling analyses and effect-modeling analyses did not show heterogeneity in the treatment effect (Figs. S5, S6, and S7 and Tables S14 and S15).

SECONDARY OUTCOME

Cardiovascular collapse during intubation occurred in 260 of 1176 patients (22.1%) in the ketamine group and in 202 of 1189 patients (17.0%) in the etomidate group (risk difference, 5.1 percentage points; 95% CI, 1.9 to 8.3) (Table 3, Fig. S8, and Table S16). Among the patients with sepsis or septic shock, cardiovascular collapse occurred in 30.6% of the patients in the ketamine group and in 20.9% of those in the etomidate group (risk difference, 9.7 percentage points; 95% CI, 4.6 to 14.9). Among the patients with a high severity of illness (defined by an Acute Physiology and Chronic Health Evaluation [APACHE] II score of ≥20; scores range from 0 to 71, with higher scores indicating a greater severity of illness), cardiovascular collapse occurred in 31.4% of the patients in the ketamine group and in 20.7% of those in the etomidate group (risk difference, 10.7 percentage points; 95% CI, 5.5 to 16.0) (Fig. S9).

EXPLORATORY OUTCOMES

The median lowest systolic blood pressure during the interval between induction of anesthesia and 2 minutes after tracheal intubation was 112 mm Hg (interquartile range, 92 to 138) in the ketamine group and 118 mm Hg (interquartile range, 98 to 141) in the etomidate group (median difference, −6; 95% CI, −9 to −1) (Table 3 and Fig. S10). A total of 164 of 1138 patients (14.4%) in the ketamine group and 123 of 1156 patients (10.6%) in the etomidate group had a systolic blood pressure below 80 mm Hg during the interval between induction of anesthesia and 2 minutes after tracheal intubation (risk difference, 3.8 percentage points; 95% CI, 1.1 to 6.5). A decrease in systolic blood pressure of more than 30 mm Hg during this period occurred in 265 of 1109 patients (23.9%) in the ketamine group and in 165 of 1126 patients (14.7%) in the etomidate group (risk difference, 9.2 percentage points; 95% CI, 6.0 to 12.5).

The median time from induction of anesthesia to successful intubation was 112 seconds (interquartile range, 86 to 155) in the ketamine group, as compared with 103 seconds (interquartile range, 80 to 134) in the etomidate group (median difference, 9; 95% CI, 5 to 14). The median number of ventilator-free days, vasopressor-free days, and ICU-free days appeared to be similar in the two groups, as did the remaining exploratory outcomes (Table 3; Tables S17, S18, and S19; and Fig. S11).

SAFETY OUTCOMES

Ventricular tachycardia during the interval between induction of anesthesia and 2 minutes after intubation (a post hoc outcome added after the enroll-

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ketamine (N=1176)	Etomidate (N=1189)
Median age (IQR) — yr	60 (45–69)	60 (44–69)
Female sex — no. (%)	498 (42.3)	492 (41.4)
Race or ethnic group — no. (%)†		
Non-Hispanic White	686 (58.3)	706 (59.4)
Non-Hispanic Black	300 (25.5)	287 (24.1)
Hispanic	130 (11.1)	132 (11.1)
Other	60 (5.1)	64 (5.4)
Median weight (IQR) — kg	78.9 (65.1–95.6)	78.5 (65.3–93.3)
Median body-mass index (IQR)‡	26.9 (23.0–32.4)	26.7 (22.5–32.1)
Location of intubation — no. (%)		
Emergency department	663 (56.4)	655 (55.1)
Intensive care unit	513 (43.6)	534 (44.9)
Chronic conditions — no. (%)		
Adrenal insufficiency or long-term receipt of glucocorticoids	136 (11.6)	129 (10.8)
Cirrhosis	165 (14.0)	166 (14.0)
Congestive heart failure	175 (14.9)	158 (13.3)
Coronary artery disease	141 (12.0)	153 (12.9)
Hypertension	536 (45.6)	533 (44.8)
Cancer	227 (19.3)	215 (18.1)
Acute conditions — no. (%)§		
Acute cardiac condition¶	216 (18.4)	223 (18.8)
Acute respiratory condition‖	678 (57.7)	683 (57.4)
Acute neurologic condition**	125 (10.6)	121 (10.2)
Sepsis or septic shock††	539 (45.8)	565 (47.5)
Median Glasgow Coma Scale score (IQR)‡‡	11 (7–15)	11 (7–15)
Median APACHE II score (IQR)§§	18 (13–24)	18 (13–24)
Median highest heart rate within 1 hr before enrollment (IQR) — beats per min	107 (90–125)	108 (92–126)
Median lowest systolic blood pressure within 1 hr before enrollment (IQR) — mm Hg¶¶	115 (96–136)	114 (94–135)
Receipt of vasopressors within 1 hr before enrollment — no. (%)	246 (20.9)	274 (23.0)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race and ethnic group were reported by the patients or their surrogates as part of clinical care and were obtained from the electronic health record by research personnel and grouped into fixed categories.
‡ Data on body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for 19 patients (0.8%): 8 in the ketamine group and 11 in the etomidate group.
§ Data on acute conditions were abstracted from the electronic health record and grouped into prespecified categories. Patients could have had more than one acute condition.
¶ Acute cardiac condition was defined as the presence of one or more of the following conditions at the time of enrollment: cardiac arrest, cardiogenic shock, congestive heart failure, cardiogenic pulmonary edema, pulmonary hypertension, or myocardial infarction.
‖ Acute respiratory condition was defined as the presence of one or more of the following conditions at the time of enrollment: acute respiratory distress syndrome, hypercapnic respiratory failure, hypoxemic respiratory failure, or pneumonia.
** Acute neurologic condition was defined as the presence of one or more of the following conditions at the time of enrollment: intracranial bleeding, meningitis, encephalitis, or stroke.
†† Sepsis or septic shock at enrollment was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).
‡‡ Glasgow Coma Scale scores range from 3 to 15, with lower scores indicating a lower level of consciousness. Glasgow Coma Scale scores were missing for 10 patients (0.4%): 6 in the ketamine group and 4 in the etomidate group.
§§ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating a greater severity of illness.
¶¶ Data on the lowest systolic blood pressure within 1 hour before enrollment were missing for 22 patients (0.9%): 11 in the ketamine group and 11 in the etomidate group.

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Table 2. Characteristics of the Intubation Procedure.

Characteristic	Ketamine (N=1176)	Etomidate (N=1189)	Difference (95% CI)*
Primary medication for induction of anesthesia — no. (%)†			
Ketamine	1167 (99.2)	3 (0.3)	99.0 (98.4 to 99.6)
Etomidate	6 (0.5)	1184 (99.6)	–99.1 (–99.6 to –98.5)
None	3 (0.3)	2 (0.2)	0.1 (–0.3 to 0.5)
Neuromuscular blocking agent — no. (%)‡			
Rocuronium	810 (69.0)	819 (69.0)	0.0 (–3.7 to 3.7)
Succinylcholine	362 (30.8)	365 (30.7)	0.1 (–3.6 to 3.8)
None	3 (0.3)	3 (0.3)	0.0 (–0.4 to 0.4)
Measurements or treatments at induction of anesthesia			
Median oxygen saturation (IQR) — %§	99 (97–100)	99 (97–100)	0 (–1 to 1)
Preoxygenation — no. (%)	1172 (99.7)	1186 (99.7)	–0.1 (–0.5 to 0.4)
Median systolic blood pressure (IQR) — mm Hg¶	127 (110–147)	127 (110–148)	0 (–3 to 3)
Vasopressor bolus or increased infusion rate — no. (%)	207 (17.6)	234 (19.7)	–2.1 (–5.2 to 1.1)
Laryngoscope used on the first attempt — no. (%)			
Video	1124 (95.6)	1127 (94.8)	0.8 (–0.9 to 2.5)
Direct	49 (4.2)	60 (5.0)	–0.9 (–2.6 to 0.8)
Other‖	3 (0.3)	2 (0.2)	0.1 (–0.3 to 0.5)
Instrument used on the first intubation attempt — no. (%)**			
Endotracheal tube with stylet	672 (57.3)	689 (58.1)	–0.8 (–4.7 to 3.2)
Bougie	455 (38.8)	446 (37.6)	1.2 (–2.7 to 5.1)
Neither endotracheal tube with stylet nor bougie	45 (3.8)	51 (4.3)	–0.5 (–2.1 to 1.1)

* For categorical variables, the unadjusted difference in the percentage is reported in percentage points, and for continuous variables, the unadjusted difference in the median value is reported.

† One patient in the ketamine group received ketamine and then also received etomidate as a second induction medication. A total of 35 patients (1.5%) received either propofol or a benzodiazepine in addition to ketamine or etomidate: 18 in the ketamine group and 17 in the etomidate group. A total of 5 patients had hemodynamic instability or cardiac arrest before induction and underwent intubation without an induction medication: 3 in the ketamine group and 2 in the etomidate group.

‡ One patient in the ketamine group received both rocuronium and succinylcholine. Data on neuromuscular blocking agents were missing in 4 patients (0.2%): 2 in the ketamine group and 2 in the etomidate group.

§ Data on oxygen saturation at induction were missing in 108 patients (4.6%): 54 in the ketamine group and 54 in the etomidate group.

¶ Data on systolic blood pressure at induction were missing in 112 patients (4.7%): 59 in the ketamine group and 53 in the etomidate group.

‖ Three patients in the ketamine group and 2 patients in the etomidate group underwent intubation with the use of a bronchoscope or an intubating laryngeal mask airway.

** Among the 2360 patients who underwent intubation with a laryngoscope, data on the instrument that was used on the first attempt were missing in 2 patients (0.1%): 1 in the ketamine group and 1 in the etomidate group.

ment of the first 567 patients) occurred in 9 of 884 patients (1.0%) in the ketamine group and in 2 of 905 patients (0.2%) in the etomidate group (risk difference, 0.8 percentage points; 95% CI, 0.1 to 1.5) (Table S20). A total of 420 of 1079 patients (38.9%) in the ketamine group and 458 of 1082 patients (42.3%) in the etomidate group were receiving vasopressors at 24 hours after enrollment (risk difference, –3.4 percentage points; 95% CI, –7.5 to 0.7).

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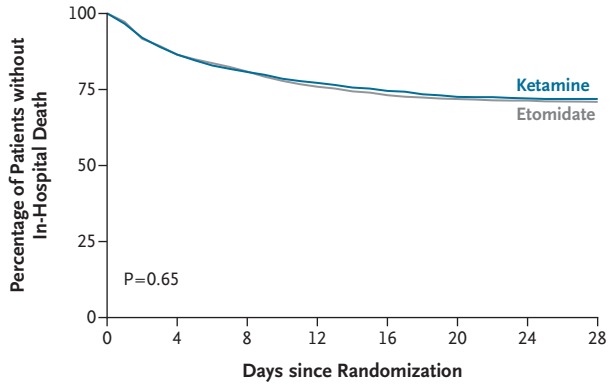

Figure 1. In-Hospital Death, According to Trial Group.

Shown is the percentage of patients without in-hospital death from enrollment through day 28. The incidence of in-hospital death by day 28 (the primary outcome) did not differ significantly between the ketamine group (28.1%) and the etomidate group (29.1%) (risk difference adjusted for trial site, −0.8 percentage points; 95% CI, −4.5 to 2.9; P=0.65 by a generalized linear mixed-effects model with a random effect for trial site).

DISCUSSION

Among critically ill adults undergoing emergency tracheal intubation in this multicenter, randomized trial, the use of ketamine for induction of anesthesia did not result in a significantly lower incidence of death than etomidate. The incidence of cardiovascular complications during intubation appeared to be higher with ketamine than with etomidate. These findings are important, given the concern that etomidate-induced corticosteroid insufficiency could affect a patient's risk of death — a concern that has led regulators to limit the availability of etomidate and has led clinicians to treat patients with induction medications that are more likely to lead to hemodynamic instability.

Numerous studies have shown that the use of etomidate to induce anesthesia impairs cortisol production for up to 72 hours.[14-19] Whether this impairment in cortisol production increases the risk of death, however, has been unclear.[55,56] In large observational studies, a lower risk of death was observed among critically ill adults who received ketamine than among those who received etomidate.[7,17] Previous randomized trials have shown inconclusive results. Among 801 patients at a single center in a recent trial, the incidence of death by day 7 was 7.8 percentage points (95% CI, 2.4 to 13.0) lower with ketamine than with etomidate, but the incidence of death by day 28 did not differ significantly between the groups.[41] In a previous multicenter trial involving 469 patients, the incidence of death by day 28 did not differ significantly between the group that received ketamine and the group that received etomidate, but the incidence of organ dysfunction and death appeared to be lower in the ketamine group than in the etomidate group among patients with sepsis.[18] Two recent meta-analyses that included data from all 2384 patients who had been enrolled in previous randomized trials reached differing conclusions, with one showing that the use of ketamine probably led to a lower risk of death than etomidate[43] and one showing no difference.[44]

The concern stemming from these earlier studies that the use of etomidate might increase patients' risk of death has led to the removal of etomidate from the market in some countries[23-25] and to recommendations against its use in some guidelines.[29] Among the 2365 patients in the current trial — approximately as many patients as were included in the aforementioned previous randomized trials combined — we observed no significant difference in the incidence of death between the ketamine and etomidate groups at any time point or in any subgroup.

One reason that ketamine has been increasingly used for induction of anesthesia in critically ill adults[7,26,27] is the perception that ketamine maintains hemodynamic stability during intubation better than other induction medications.[24,28,29] Some experts specifically recommend ketamine for intubation of patients with sepsis or those who are receiving vasopressors.[24,29,57,58] Our trial showed that hypotension, receipt of vasopressors, and ventricular tachycardia during intubation each appeared to be more common with ketamine than with etomidate. These effects appeared to be largest among patients with sepsis and among those receiving vasopressors. Although discordant with the recommendations in some guidelines,[29] these findings are concordant with the results of two observational studies and one previous randomized trial, each of which showed a higher incidence of cardiovascular complications with ketamine than with etomidate.[33,34,41]

Our trial has several strengths. The design included randomization to balance baseline characteristics, enrollment of a large sample of pa-

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Table 3. Outcomes.

Outcome	Ketamine (N=1176)	Etomidate (N=1189)	Difference (95% CI)*
Primary outcome: in-hospital death from any cause by day 28 — no. (%)†	330 (28.1)	345 (29.1)	–0.8 (–4.5 to 2.9)‡
Secondary outcome: cardiovascular collapse during the interval between induction of anesthesia and 2 minutes after intubation — no. (%)	260 (22.1)	202 (17.0)	5.1 (1.9 to 8.3)
Systolic blood pressure <65 mm Hg§	73 (6.4)	64 (5.5)	0.9 (–1.0 to 2.8)
Receipt of a new or increased dose of vasopressors	251 (21.3)	189 (15.9)	5.4 (2.3 to 8.6)
Cardiac arrest¶	12 (1.0)	10 (0.8)	0.2 (–0.6 to 1.0)
Exploratory procedural outcomes			
Median lowest systolic blood pressure (IQR) — mm Hg§	112 (92–138)	118 (98–141)	–6 (–9 to –1)
Lowest systolic blood pressure <80 mm Hg — no. (%)§	164 (14.4)	123 (10.6)	3.8 (1.1 to 6.5)
Median highest systolic blood pressure (IQR) — mm Hg§	140 (115–164)	141 (118–168)	–2 (–7 to 2)
Highest systolic blood pressure >180 mm Hg — no. (%)§	154 (13.5)	191 (16.5)	–2.9 (–5.9 to 0.0)
Median lowest oxygen saturation (IQR) — %‖	97 (90–100)	97 (89–100)	0 (0 to 2)
Lowest oxygen saturation <80% — no. (%)‖	125 (11.1)	126 (11.1)	0.0 (–2.6 to 2.6)
Successful intubation on the first attempt — no. (%)**	1005 (85.7)	1029 (86.7)	–1.0 (–3.8 to 1.8)
Median time from induction of anesthesia to intubation (IQR) — sec††	112 (86–155)	103 (80–134)	9 (5 to 14)
Exploratory clinical outcomes†‡‡			
Median ventilator-free days (IQR)	23 (0–26)	23 (0–26)	0 (–1 to 1)
Median vasopressor-free days (IQR)	25 (0–28)	25 (0–28)	0 (–1 to 1)
Median ICU-free days (IQR)	20 (0–24)	19 (0–24)	1 (–1 to 2)
Safety outcomes			
Median systolic blood pressure at 24 hours (IQR) — mm Hg§§	114 (102–130)	114 (103–129)	0 (–2 to 3)
Ongoing receipt of vasopressors at 24 hours — no. (%)¶¶	420 (38.9)	458 (42.3)	–3.4 (–7.5 to 0.7)

* For the primary outcome, the absolute risk difference with adjustment for trial site, which was generated with the use of a general linear mixed-effects model with a random effect for trial site without adjustment for covariates, is shown. For other outcomes, the unadjusted absolute risk difference in the percentage is reported in percentage points for categorical variables, and the unadjusted difference in the median value is reported for continuous and ordinal variables; the widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two groups.

† A total of 6 patients (0.3%) withdrew from follow-up before day 28 and were missing data for 28-day outcomes: 3 in the ketamine group and 3 in the etomidate group.

‡ P=0.65.

§ Data on systolic blood pressure during the interval between induction of anesthesia and 2 minutes after intubation were missing for 68 patients (2.9%): 38 in the ketamine group and 30 in the etomidate group.

¶ Of the 22 patients (0.9%) who had cardiac arrest during the interval between induction of anesthesia and 2 minutes after intubation, 5 (0.2%) died within 1 hour after intubation: 3 in the ketamine group and 2 in the etomidate group.

‖ Data on the oxygen saturation during the interval between induction of anesthesia and 2 minutes after intubation were missing for 106 patients (4.5%): 49 in the ketamine group and 57 in the etomidate group.

** This analysis includes the 2360 patients who underwent intubation with a laryngoscope.

†† Data on the time from induction of anesthesia to intubation were missing for 26 patients (1.1%): 14 in the ketamine group and 12 in the etomidate group.

‡‡ Ventilator-free days, vasopressor-free days, and ICU-free days were assessed at 28 days, with follow-up data censored at the time of hospital discharge.

§§ Data on systolic blood pressure at 24 hours after enrollment were unavailable for the 204 patients (8.6%) who died or were discharged before 24 hours. These data were missing for 9 patients (0.4%): 4 in the ketamine group and 5 in the etomidate group.

¶¶ Data on the ongoing receipt of vasopressors at 24 hours after enrollment were unavailable for the 204 patients (8.6%) who died or were discharged before 24 hours; 97 were in the ketamine group and 107 were in the etomidate group. Among the 878 patients who were receiving vasopressors at 24 hours after enrollment, the median vasopressor dose in norepinephrine equivalents (a post hoc outcome) was 0.09 μg per kilogram per minute (IQR, 0.04 to 0.20) in the ketamine group and 0.12 μg per kilogram per minute (IQR, 0.06 to 0.27) in the etomidate group (median difference, –0.03; 95% CI, –0.06 to –0.01).

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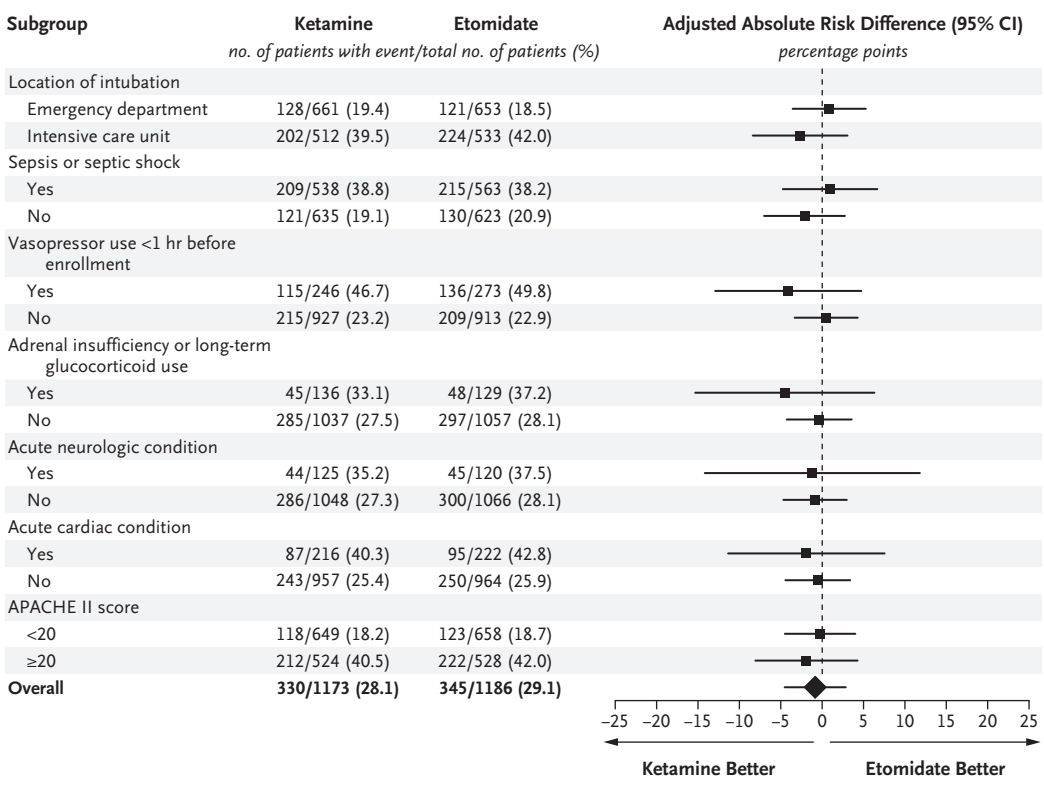
Subgroup
Ketamine
Etomidate
Adjusted Absolute Risk Difference (95% CI)
no. of patients with event/total no. of patients (%)
percentage points
Location of intubation
Emergency department 128/661 (19.4) 121/653 (18.5)
Intensive care unit 202/512 (39.5) 224/533 (42.0)
Sepsis or septic shock
Yes 209/538 (38.8) 215/563 (38.2)
No 121/635 (19.1) 130/623 (20.9)
Vasopressor use <1 hr before enrollment
Yes 115/246 (46.7) 136/273 (49.8)
No 215/927 (23.2) 209/913 (22.9)
Adrenal insufficiency or long-term glucocorticoid use
Yes 45/136 (33.1) 48/129 (37.2)
No 285/1037 (27.5) 297/1057 (28.1)
Acute neurologic condition
Yes 44/125 (35.2) 45/120 (37.5)
No 286/1048 (27.3) 300/1066 (28.1)
Acute cardiac condition
Yes 87/216 (40.3) 95/222 (42.8)
No 243/957 (25.4) 250/964 (25.9)
APACHE II score
<20 118/649 (18.2) 123/658 (18.7)
≥20 212/524 (40.5) 222/528 (42.0)
Overall 330/1173 (28.1) 345/1186 (29.1)
−25 −20 −15 −10 −5 0 5 10 15 20 25
Ketamine Better
Etomidate Better

Figure 2. Subgroup Analyses of the Primary Outcome.

Shown are the absolute risk differences and 95% confidence intervals with adjustment for trial site for in-hospital death by day 28 (the primary outcome) in the ketamine group as compared with the etomidate group in each prespecified subgroup. Differences between the ketamine group and the etomidate group were calculated with the use of a generalized linear mixed-effects model with a random effect for trial site and fixed effects for trial group, the proposed effect modifier, and the interaction between the trial group and the proposed effect modifier without adjustment for covariates. Differences of less than 0 indicate a lower likelihood of death with the use of ketamine. Sepsis or septic shock at enrollment was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Chronic glucocorticoid use was defined as receipt of glucocorticoids for at least 3 consecutive weeks before enrollment. An acute neurologic condition was defined as active intracranial bleeding, meningitis, encephalitis, or stroke. An acute cardiac condition was defined as active cardiac arrest, cardiogenic shock, congestive heart failure, cardiogenic pulmonary edema, pulmonary hypertension, or myocardial infarction. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score ranges from 0 to 71, with higher scores indicating a greater severity of illness. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two groups.

tients to provide sufficient statistical power to detect clinically meaningful differences between the trial groups in the incidence of death, and conduct of the trial in EDs and ICUs at multiple centers to increase generalizability. The trial population had a sufficiently high severity of illness (nearly 30% of the patients died by day 28) and a sufficiently large number of patients with sepsis or septic shock (more than 1100) or who were receiving vasopressors (more than 500) to credibly evaluate the hypothesized relationship between receipt of etomidate and death. Adherence to the trial-group assignments was excellent, and the percentage of patients with missing data for the primary outcome was low.

Our trial also has limitations. The trial excluded patients who presented with a primary diagnosis of trauma, so the results may not apply to such patients. Because the trial was not blinded, awareness of the trial-group assignments could have

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influenced the trained observers' assessments of intraprocedural outcomes or clinicians' subsequent treatment decisions. Our findings do not rule out the possibility of small differences in outcomes in favor of either ketamine or etomidate, and for such commonly used medications, even small differences in outcomes might be clinically meaningful. Our trial compared ketamine and etomidate, so the results do not inform the effectiveness or safety of other induction medications, such as propofol, benzodiazepines, or barbiturates.

Among critically ill adults undergoing tracheal intubation, the use of ketamine to induce anesthesia did not lead to a significantly lower incidence of in-hospital death by day 28 than etomidate.

The views and statements presented in this article are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute or the National Institutes of Health.

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